REMARKS

Claims 6-22 and 24-29 are pending and under examination. Claim 14 has been amended.

Support for claim 14 as amended may be found, *inter alia,* on page 33, lines 22-32. Applicants maintain that the amendment does not raise an issue of new matter. Entry of this Amendment is respectfully requested.

WO 02/100341 has been made of record. See July 19, 2005 IDS and the initialed Form PTO-1449 enclosed with the November 7, 2006 Office Action. The attention of the Examiner is directed to Formula CVIII in Scheme 27 of WO 02/100341 (page 94). WO 02/100341 discloses Formula CVIII as a synthetic intermediate. WO 02/100341 does not disclose any biological activity for compounds of Formula CVIII, nor does WO 02/100341 disclose compounds of Formula CVIII in purified form or administering such compounds to any mammal.

NO DOUBLE PATENTING

Claims 6-22 and 24-29 have been provisionally rejected for alleged obviousness-type double patenting over claims 6-22 of copending Application No. 10/533,936 [sic, 10/553,936] (the '936 application), claims 6-22 of copending Application No. 11/554,586 [sic, 10/554,586] (the '586 application) and claims 1-66 of copending Application No. 11/535,779 (the '779 application) in view of U.S. Patent No. 5,604,225 (Reiffen), U.S. Patent No. 6,156,781 (Talley), U.S. Patent No. 5,665,387 (Mathieu), and Patent Publication No. US 2002/0028943. The double patenting rejections are respectfully traversed.

Neither Application No. 10/533,936 nor Application No. 11/554,586 is jointly owned with the subject application. Applicants believe that these are typographical errors and that "10/553,936" and "10/554,586" were intended, respectively.

Application No. 10/553,936 issued as U.S. Patent No. 7,361,686 (the '686 patent) on April 22, 2008. Accordingly the obviousness-type double patenting rejection over the '936 application is no longer a provisional rejection.

The '586 application and the '779 application were filed after the subject application. Accordingly, upon an indication of otherwise allowable subject matter the provisional obviousnesss-type double patenting rejections should be withdrawn and the subject application should be allowed to issue as a patent without a terminal disclaimer over the copending applications. MPEP §804(I)(B)(1), Rev. 5, Aug. 2006, page 800-17, right column.

Moreover, the subject application is patentably distinct from each of the primary reference patent documents in view of the secondary references.

Patentably Distinct From Application No. 10/553,936 (Patent No. 7,361,686)

The claims in the '686 patent application recite compounds having an alkenyl double bond in the backbone of the molecule instead of a hydroxy substituent. The rejection relies on U.S. Patent No. 5,604,225 (Reiffen, et al.) and U.S. Patent No. 6,156,781 (Talley, et al.) for the proposition that hydroxy-substitution and an alkenyl double bond are obvious variants.

The substitution of the tetrahedral alcohol (i.e. hydroxy) for the planar alkenyl alters the geometry, the H-bonding properties and the charge distribution of the molecule. Alcohols have both H-bond donor and acceptor properties, while an alkenyl double bond has neither. Therefore it could not have been reasonably predicted that the hydroxy-substituted compounds of the present invention would possess the same activity as the reference compounds.

The rejection relies on the teaching of Reiffen that substituent R_4 can be, among other things, hydroxyl or alkenyl. But this teaching of Reiffen is not analogous to the difference between the compounds of the present invention and those of Reiffen. R_4 of Reiffen is a substituent. In the case where R_4 is alkenyl it is an alkenyl substituent. But in the '936 application the alkenyl is not a substituent. Rather it is a double bond in the backbone of the molecule, turning what would otherwise be an alkanoic acid moiety into an alkenyl acid moiety. Thus the alkenyl of Reiffen relied upon by the rejection is not analogous to or probative of the instant rejection. Moreover, Reiffen discloses a genus of compounds with a large number of variables. Reiffen did not test even a single compound for any activity.

The reliance of the rejection on Talley is similarly misplaced. Talley teaches that R^4 can be substituted by, among other things, hydroxyl or alkenyl. But this teaching of Talley is not analogous to the difference between the compounds of the instant invention and those of Talley. The alkenyl mentioned in the passage of Talley cited in the rejection is an alkenyl substituent. In conrast, in the '936 application the alkenyl is not a substituent. Rather it is a double bond in the backbone of the molecule, turning what would otherwise be an alkanoic acid moiety into an alkenyl acid moiety. Thus the alkenyl of Talley relied upon by the rejection is not analogous to or probative of the instant rejection.

Based on the nonanalogous teachings of Reiffen and Talley, applicants submit that the person of ordinary skill in the art would not have had a reasonable expectation of success from changing an alkenyl double bond in the backbone of the molecule as in the '936 application to a single bond in the backbone of the molecule and adding a hydroxy substituent.

The preceding argument was presented in applicants' May 7, 2007 Communication in response to the November 7, 2006 Office Action. The rejection now states,

> "Applicants' remarks regarding the obviousness-type double patenting are not persuasive because the applicants at the time could substitute alkyl, hydroxyl and keto with each other with the expectation that the

> substitution would not significantly alter the analogous properties of the compound due to close structural similarity of the compounds."

(November 30, 2007 Office Action, pp. 3-4). As seen from the above-quoted passage the rejection does not even try to defend the proposition that hydroxy-substitution and an alkenyl double bond are obvious variants.

Patentably Distinct from Application No. 10/554,586 and No. 11/535,779

The claims in the '586 application differ from the claims of the instant application in two ways. First, they are not hydroxy-substituted at the position adjacent to the central phenyl ring. Second, they are keto-substituted at the alpha position of the alkanoic acid. The claims in the '586 application recite compounds that are not hydroxy-substituted at the position adjacent to the central ring, but are keto-substituted at various positions.

The rejection relies on Patent Publication No. US 2002/0028943 (Griffin) and U.S. Patent No. 5,665,387 (Mathieu, et al.) for the proposition that alkyl, hydroxyl and keto are obvious equivalents.

Griffin discloses an enormously large genus of compounds with many variables. The passage cited by the rejection is nothing more than Griffin's definition of "substituted alkyl". Griffin did not test even a single compound for any activity. Accordingly, the disclosures of Griffin on which the rejection relies are purely hypothetical.

Mathieu discloses the use of certain vitamin D analogues for treating autoimmune diseases such as Type 1 diabetes. Mathieu discloses a general formula with many variables and values for such variables. Mathieu actually tested two compounds: 1,25 Dihydroxy-Vitamin D3 ($1,25(OH)_2D_3$) and KH1060 ($1\alpha,25(OH)_2$-20-epi-22-oxa-24,26,27-trishomo vitamin D). But Mathieu did not test analogous compounds in which the only difference is that one is substituted by hydroxyl and the other is substituted by oxo at the same position.

In contrast, compounds in which the hydroxy analog of an oxo compound was actually demonstrated to lack the activity of the oxo compound were well known. Examples may be found in the scientific literature of record, as follows:
Connolly, et al., J. Med. Chem. (2002) 45: 1348-1362.
Flynn, et al., J. Med. Chem. (2002) 45: 2670-2673.

Compounds **22** and **41** of Connolly (Table 6 on page 1355) are analogous compounds. In compound **22**, X and Y together are =O. In compound **41** X is H and Y is OH. Connolly tested the ability of various compounds to inhibit Cytosolic Phospholipase A_2. Connolly found that "Simple changes to the highly potent keto-acid **22**, such as . . . reduction (**41** and **42**) . . . largely destroy activity (see Table 6)." (Connolly, page 1355, left column, last paragraph) (bolding in original).

Compounds **9** and **20** of Flynn (Table 1 on page 2671) are analogous compounds. In compound **9** Y is C=O. In compound **20** Y is CH(OH). The compounds shown in Table 1 "were evaluated for inhibition of tubulin assembly (Table 1). Those that displayed a significant inhibitory effect (defined as $IC_{50} < 5.0$ μM) were also examined for an inhibitory effect on the binding of [^{3}H]colchicine to tubulin. . . . These compounds were also evaluated for cytotoxicity against MCF-7 human breast carcinoma cells (Table 1)." (Flynn, page 2672, left column, first full paragraph). "Compound **9** was the most active" of all compounds tested in the inhibition of tubulin polymerization test. (Flynn, page 2672, second full paragraph. See also Table 1) (bolding in original). In contrast compound **20** had an $IC_{50} > 40$ μM, which did not meet the criteria for significant inhibitory effect in the inhibition of tubulin polymerization test. Similarly in the inhibition of MCF-7 cell growth test compound 9 had an IC_{50} of 34 ± 10 nM, whereas compound **20** had an $IC_{50} > 1000$ nM.

The person of ordinary skill in the art would have given greater credence to the actual experimental evidence of nonequivalence in compounds differing only in having hydroxy or oxo at the same position as shown in Connolly et al. and Flynn et al. than to the

hypothetical teachings of equivalence in Griffin et al. or to the less probative examples of Mathieu et al. Accordingly, the person of ordinary skill would not have predicted that the hydroxy-substituted compounds of the present invention would possess the same activity as their oxo-substituted analogs claimed in the '586 application and the '779 application with a reasonable expectation of success.

Moreover there are good theoretical reasons for not necessarily expecting oxo and hydroxy to be interchangeable. The substitution of the tetrahedral alcohol (i.e. hydroxy) for the planar carbonyl (i.e. oxo or keto) group alters the geometry, the H-bonding properties and the charge distribution of the molecule. Alcohols have both H-bond donor and acceptor properties, while an oxygen functionality at the final position of the acid acts as an H-bond acceptor but not as an H-bond donor. Therefore it could not have been reasonably predicted that the hydroxy-substituted compounds of the present invention would possess the same activity as their oxo-substituted analogs claimed in the '586 application and the '779 application.

The preceding argument was presented in applicants' May 7, 2007 Communication in response to the November 7, 2006 Office Action. The rejection now states,

> "Applicants' remarks regarding the obviousness-type double patenting are not persuasive because the applicants at the time could substitute alkyl, hydroxyl and keto with each other with the expectation that the substitution would not significantly alter the analogous properties of the compound due to close structural similarity of the compounds."

(November 30, 2007 Office Action, pp. 3-4). But, of course, merely asserting that such substitutions would be expected to not significantly alter the properties of the compound does not make it so. Applicants have presented both theoretical arguments and actual examples demonstrating that substitutions of the sort in question can indeed significantly affect the properties of, otherwise structurally identical compounds. The rejection nowhere explains why, in the face of the evidence presented, the person of skill in the art allegedly would have expected that these substitutions would not significantly alter the properties of the compound.

In view of the foregoing, applicants respectfully submit that the obviousness-type double patenting rejections have been overcome.

INVENTION IS ENABLED

Claims 6-11 and 13-18 have been rejected under 35 USC 112, first paragraph, as allegedly not being enabled by the specification. The rejection is respectfully traversed.

The Office acknowledges that the specification is "enabling for treating Type II diabetes". (November 30, 2007 Office Action, page 4). The basis of the rejection is that the specification allegedly is not enabling for treating "all types of diabetes such as Type I and gestational diabetes." (See November 30, 2007 Office Action, page 5).

Pharmaceutical Composition (Claims 14-18) is Enabled

"[W]hen a compound or composition claim is not limited by a recited use, any enabled use that would reasonably correlate with the entire scope of that claim is sufficient to preclude a rejection for nonenablement based on how to use." MPEP §2164.01(c), Rev. 6, sept. 2007, page 2100-195, right column, last paragraph. See also In re Brana, 51 F.3d 1560, 34 USPQ.2d 1436 (Fed. Cir. 1995); Cross v. Iizuka, 753 F.2d 1040, 224 USPQ 739 (Fed. Cir. 1985); Application of Krimmel, 48 CCPA 1116, 292 F.2d 948, 130 USPQ 215 (1961). Claims 14-18 are not limited by a recited use and it is undisputed that the specification provides an enabled use. Therefore a rejection for nonenablement based on how to use is improper.

Claims 14-18 are directed to a pharmaceutical composition and do not recite any specific conditions. Accordingly, claims 14-18 are not limited by a recited use.

The rejection acknowledges that the specification is ""enabling for treating Type II diabetes". (November 30, 2007 Office Action, page 4). Accordingly the Office accepts that there is an enabled use. The enablement provision of Section 112, first paragraph, requires nothing more.

Method of Treatment (Claims 6-11, 13) is Enabled

The Office bears the burden of establishing that an invention does not satisfy the enablement requirement of 35 U.S.C. §112, first paragraph. As stated by the CCPA in In re Marzocchi:

"As a matter of Patent Office practice, then, a specification disclosure which contains a teaching of the manner and process of making and using the invention in terms which correspond in scope to those used in describing and defining the subject matter sought to be patented must be taken as in compliance with the enabling requirement of the first paragraph of § 112 unless there is reason to doubt the objective truth of the statements contained therein which must be relied on for enabling support."

(In re Marzocchi, 439 F.2d 220, 223, 169 USPQ 367, ___ (CCPA 1971)) (underlining added). It is not sufficient for the Office to simply assert that it doubts the correctness of the statements in the disclosure. The Office must back up its doubts with evidence or reasoning. Again from In re Marzocchi:

"In any event, it is incumbent upon the Patent Office, whenever a rejection on this basis is made, to explain why it doubts the truth or accuracy of any statement in a supporting disclosure and to back up assertions of its own with acceptable evidence or reasoning which is inconsistent with the contested statement."

(In re Marzocchi, 439 F.2d at 224, 169 USPQ at ___) (internal citations omitted) (underlining added). The only reasoning presented by the rejection is: (1) the alleged

lack of working examples showing the treatment of Type I diabetes and gestational diabetes; and (2) the alleged failure to provide guidance as to how the invention works to treat all types of diabetes.

With regard to working examples, the rejection states, "The working examples are limited to the administration of instant compounds of formula I to treat Type II diabetes only. No examples showing to treat type I diabetes or gestational diabetes." (November 30, 2007 Office Action, page 6). But, of course, a specification can be enabling without any working examples. Gould v. Quigg, 822 F.2d 1074, 1078 (Fed. Cir. 1987).

With regard to how the invention works, the rejection states, "Applicants have failed to provide guidance as to how the other instant compounds of formula I is [sic] effective in treating all types of diabetes." (November 30, 2007 Office Action, page 6). That is an improper basis upon which to base an enablement rejection since "it is axiomatic that an inventor need not comprehend the scientific principles on which the practical effectiveness of his invention rests, nor is the inventor's theory or belief as to how his invention works a necessary element in the specification to satisfy the enablement requirement of 35 U.S.C. §112." Cross v. Iizuka, 753 F.2d 1040, 1042, 224 USPQ 739, ____ (Fed. Cir. 1985), citing Fromson v. Advance Offset Plate, Inc., 720 F.2d 1565, 1570, 219 USPQ 1137, 1140 (Fed. Cir. 1983).

Contrary to the basis of the rejection, the established relationship between Type 2 diabetes and gestational diabetes supports the enablement of this invention as claimed. Friedman, et al. report:

> "Women who develop gestational diabetes mellitus (GDM) have severe insulin resistance and markedly increased risk to develop subsequent type 2 diabetes.
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> * * * * * * * * *
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> "GDM [gestational diabetes mellitus] shares many of the characteristics of type 2 diabetes. Both are aggravated by increasing obesity and age, suggesting that components of insulin resistance and decreased insulin secretion, which lead to GDM, may be common to type 2 diabetes. Thus,

> GDM may represent an unmasking of the genetic predisposition toward type 2 diabetes induced by the hormonal changes of pregnancy."

(Friedman, et al., Diabetes (Sept. 1999) 48: 1807-1814 at 1807) (copy enclosed). As seen from the above-quoted passage, obesity and age are risk factors for Type 2 diabetes and for gestational diabetes. Moreover, gestational diabetes is a risk factor for developing Type 2 diabetes. Accordingly, the person of skill in the art would have no reason to doubt that the efficacy of the claimed invention in treating Type 2 diabetes would hold true for gestational diabetes as well.

Type 2 and Type 1 diabetes also share similarities. The presence of insulin resistance is associated with increased subsequent risk of vascular disease in patients with Type 1 or with Type 2 diabetes. Kilpatrick, et al. report:

> "The presence of insulin resistance and the metabolic syndrome are known risk markers for macrovascular disease in patients with and without type 2 diabetes. This study has examined whether these also were predictors of micro- and macrovascular complications in type 1 diabetic patients participating in the Diabetes Control and Complications Trial (DCCT). . . . Higher insulin resistance at baseline in the DDCCT (as estimated by eGDR) was associated with increased subsequent risk of both micro- and macrovascular complications."

(Kilpatrick, et al., Diabetes Care (March 2007) 30(3): 707-712 at Abstract, p. 707) (copy enclosed). Applicants note that the Kilpatrick article postdates the filing of the subject application. Accordingly, it is not being cited as enabling this invention, but rather as confirming applicants' position that the guidance provided in the specification holds true for Type 1 diabetes and is not limited to Type 2 diabetes as the rejection would have it. The person of skill in the art would have no reason to doubt that the efficacy of the claimed invention in treating Type 2 diabetes would hold true for Type 1 diabetes as well.

In view of the foregoing, applicants respectfully submit that the enablement rejection has been overcome.

CONCLUSION

In view of the amendments and the preceding remarks, applicants respectfully submit that the subject application is now in condition for allowance. Reconsideration and withdrawal of all rejections is respectfully requested.

No fee, other than the extension of time fee, is believed necessary in connection with the filing of this Amendment. If any additional fee is required, the Commissioner is hereby authorized to charge the amount of such fee, or to refund any overpayment, to Deposit Account No. 50-1677.

Respectfully submitted,

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